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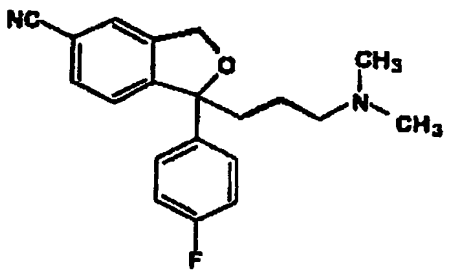
PATENT- OG VAREMÆRKESTYRELSEN

A process for the preparation of racemic citalopram diol and/or *S*- or *R*-citalopram diols and the use of such diols for the preparation of racemic citalopram, *R*-citalopram and/or *S*-citalopram

The invention relates to a process for the preparation of racemic citalopram diol and *R*- or *S*-citalopram diol by separating an initial non-racemic mixture of the compounds *R*- and *S*-citalopram diol into; a fraction of racemic citalopram diol and/or a fraction being enriched with *S*-diol or *R*-diol. The invention also relates to the use of such isolated citalopram diols for the formation of the corresponding racemic citalopram and/or *S*- or *R*-citalopram to be comprised in a pharmaceutical composition.

Background of the invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



Citalopram may be prepared by ring closure of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (racemic citalopram diol) as described in US patent No. 4,650,884. The product citalopram is a racemic mixture of the *R*- and *S*-enantiomers.

Further, the *S*-enantiomer of citalopram (escitalopram) is a valuable antidepressant of the selective serotonin reuptake inhibitor (SSRI) type. *S*-citalopram may be prepared by ring closure of *S*-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (*S*-diol) with retention of configuration as described in

EP B1 347 066. The amount of *R*-citalopram compared to *S*-citalopram in the product escitalopram should be less than 3%.

It appears from the above, that products of racemic citalopram and escitalopram with the above-mentioned enantiomeric purity are required for the preparation of pharmaceutical compositions and that racemic citalopram and escitalopram products may be prepared by ring closure of the corresponding citalopram diols. As a consequence, methods for the preparation of products of racemic diol and *S*-diol being correspondingly enantiomerically pure are required.

Processes for the preparation and purification of *R*- or *S*-diol products are available. Such processes involve for instance enantio-selective synthesis, classical resolution and chromatographic separation. Depending on the specific process and the conditions used, the enantiomeric purity of the *S*-diol product may have to be improved before the *S*-diol product will meet the above requirements.

Surprisingly, it has now been found that by using the process of the invention an expensive but apparently useless *S*-diol product being contaminated with *R*-diol may easily be converted into the two valuable products, racemic diol and *S*-diol, which meet the above requirements as regards enantiomeric purity.

More particularly, the present invention provides a precipitation process for the separation of an initial non-racemic mixture of *R*- and *S*-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of one of the enantiomers into a fraction being enriched with *S*-diol- or *R*-diol and a fraction consisting of *RS*-diol, wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol.

According to the present invention the *RS*-diol is precipitated as the free base or as an acid addition salt thereof leaving the mother liquor enriched with either the *S*- or *R*-diol. The surplus of *R*- or *S*-diol may then be isolated from the mother liquor as described below.

The process of the invention is important and very useful, in particular because it provides a convenient, cheap and efficient way to transform a mixture of *R*- and *S*-diols which does not meet the above requirements as regards enantiomeric purity into two valuable products, racemic diol and *S*-diol (or *R*-diol), which meet the above requirements as regards enantiomeric purity.

With the present invention, the process for the production of racemic citalopram and *S*-citalopram meeting the requirements of the respective marketing approvals has become more rational and more economical as regards the simplicity of the process and the utilisation of reagents and resources.

Summary of the Invention

Thus, the present invention relates to a process for the preparation of racemic diol free base or an acid addition salt thereof and/or *R*- or *S*-diol as the free base or an acid addition salt thereof by the separation of an initial non-racemic mixture of *R*- and *S*-diol with more than 50% of one of the enantiomers into a fraction being enriched with *S*-diol or *R*-diol and a fraction consisting of *RS*-diol wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol **characterized in that**

i) *RS*-diol is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor;

iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;

iib) if the precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline precipitate is obtained and the

crystalline precipitate is optionally recrystallised one or more times to form racemic diol;

iii) the mother liquor is optionally subjected to further purification and *S*-diol or *R*-diol is isolated from the mother liquor;

iv) the free bases of the diols obtained are optionally converted to acid addition salts thereof or acid addition salts of the diols obtained are optionally converted to other acid addition salts or acid addition salts of the diols obtained are optionally converted to the corresponding free bases.

According to a specific embodiment, the invention relates to a process for the preparation of racemic diol as the free base or an acid addition salt thereof using the process described above.

According to another specific embodiment, the invention relates to a process for the preparation of *S*-diol (or *R*-diol) as the free base or an acid addition salt thereof using the process described above.

According to still another specific embodiment, the invention relates to the use of the prepared racemic diol and/or *S*-diol (or *R*-diol) free base or an acid addition salt thereof for the preparation of the corresponding racemic citalopram and/or *S*-citalopram (or *R*-citalopram) free base or an acid addition salt thereof using the process described below.

Detailed description of the invention

Whenever used in this document, the *S*-diol means *S*-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl) benzonitrile.

Whenever used in this document, the *R*-diol means *R*-4-[4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl) benzonitrile.

Whenever used in this document, *RS*-diol means a mixture of *R*- and *S*-diol including a mixture with a 1:1 ratio of the *R*- and *S*-diol.

Whenever used in this document, diol enantiomer or isomer means either *S*- or *R*-diol.

Whenever used in this document, racemic diol means a 1:1 mixture of the *R*- and *S*-diols. Non-racemic mixtures of diols means mixtures which contain *R*- and *S*-diols in a ratio other than 1:1.

Whenever used in this document, citalopram enantiomer or isomer means either *S*- or *R*-citalopram.

Whenever used in this document, racemic citalopram means a 1:1 mixture of *R*- and *S*-citalopram. Non-racemic citalopram means mixtures which contain *R*- and *S*-citalopram in a ratio other than 1:1.

As used in this description, precipitation means forming a precipitate in the form of crystals, an amorphous solid or an oil from a solvent. In the present description, a precipitate means an oil, an amorphous solid or crystals.

As used herein, mother liquor means the solvent remaining after removal or separation from the precipitate.

As already mentioned, the above processes for the preparation of the citalopram molecule may result in a mixture of *R*- and *S*-citalopram which is not acceptable for pharmaceutical use. According to the present invention, a surprisingly efficient process for the preparation of racemic diol and *R*- or *S*-diol to be used for the preparation of the corresponding racemic citalopram and *R*- or *S*-citalopram has been found.

This new process involves the separation of non-racemic diol mixtures into a fraction of racemic diol and a fraction of *R*- or *S*-diol as the free base or as an acid addition salt

thereof. The fraction of racemic diol free base or an acid addition salt thereof is precipitated as an oil, an amorphous solid or in crystalline form from a solvent, and the *R*- or *S*-diol is isolated from the mother liquor of the precipitation process. Then, racemic citalopram and *R*- or *S*-citalopram may be formed from the corresponding racemic diol and *R*- or *S*-diol by ring closure.

According to one embodiment of the invention, the initial non-racemic mixture of *R*- and *S*- diol used in the process of the invention contains more than 50% of *S*-diol, or more preferred more than 70% of *S*-diol or most preferred more than 90% of *S*-diol.

Precipitation of the *RS*-diol free base may be carried out by obtaining or dissolving the non-racemic mixture of *R*- and *S*-diol in a suitable solvent, optionally by applying heat, and then allowing the solution to cool, or by cooling to below ambient temperature. The precipitate is then separated from the mother liquor, preferably by filtration or decanting.

If the precipitate is crystalline, the crystals are optionally recrystallised one or more times. Then, racemic citalopram may be formed from the racemic diol free base by ring closure. The free base of racemic citalopram may optionally be converted to an acid addition salt thereof, preferably the hydrobromide salt.

If the precipitate formed is an oil or an amorphous solid, the precipitation process may be repeated until a crystalline product is obtained. The crystals obtained are optionally recrystallised one or more times. Racemic citalopram may be formed from the racemic diol free base by ring closure. The free base of racemic citalopram is optionally converted to an acid addition salt thereof, preferably the hydrobromide salt.

An oily phase separated from the mother liquor is optionally subjected to conventional purification processes.

The *RS*-diol free base prepared according to the invention may contain a minor excess of the *S*-diol (or *R*-diol). It may thus be necessary to repeat precipitation (in particular crystallisation) the *RS*-diol free base one or more times in order to obtain racemic diol.

The mother liquors from each precipitation or crystallisation may be pooled together and the diol enantiomer contained herein may be isolated as described below.

Suitable solvents for the precipitation of the *RS*-diol free base are apolar solvents for example alkanes, such as heptane or hexane, aromatic hydrocarbons such as toluene, benzene and xylene, or polar solvents such as acetonitrile.

If necessary, crystallisation may be initiated by seeding with racemic crystalline diol free base.

The precipitation of *RS*-diol acid addition salt may be carried out by obtaining or dissolving the non-racemic mixture of *R*- and *S*-diol in a suitable solvent, if necessary by applying heating, and then adding an acid, for example as a solid, a liquid, in a solution or as a gas.

Salts such as NaCl may be added to the solution before precipitation in order to increase the ionic strength of the solution.

If crystals are formed, the crystals are separated from the mother liquor, preferably by filtration or decanting. The crystals are optionally recrystallised by dissolving the crystals in a solvent, preferably by heating, and allowing the solution to cool, or by cooling to below ambient temperature. Racemic citalopram may be formed from the crystalline racemic diol acid addition salt by ring closure. The racemic citalopram may be converted to a pharmaceutically acceptable salt thereof, preferably the HBr salt.

If the precipitate formed is not crystalline, but amorphous or an oil, the precipitation process may be repeated until a crystalline product is obtained. The crystals obtained are optionally recrystallised one or more times as described above. Racemic citalopram may be formed from the crystalline racemic diol acid addition salt by ring closure. The racemic citalopram may be converted into a pharmaceutically acceptable salt thereof, preferably the HBr salt.

An oily phase separated from the mother liquor is optionally subjected to conventional purification processes.

The *RS*-diol acid addition salt prepared according to the invention may contain a minor excess of the *S*-diol (or *R*-diol). It may thus be necessary to repeat precipitation (in particular crystallisation) the RS-diol acid addition salt one or more times in order to obtain a racemic mixture. The mother liquors from each precipitation or crystallisation may be pooled together and the diol enantiomer contained herein may be isolated as described below.

The acid used for the precipitation of a *RS*-diol acid addition salt is an acid which precipitates a mixture of *R*- and *S*-enantiomers and leaves the mother liquor enriched with either the *R*- or *S*-diol enantiomer of the diol. Suitable acids are inorganic acids such as hydrochloric acid, hydrobromic acid and sulphuric acid or organic acids such as oxalic acid. Hydrochloric acid is a preferred acid. Suitably, half an equivalent to 10 equivalents of acid is used.

Suitable solvents for the precipitation of *RS*-diol acid addition salts are polar and apolar solvents such as toluene, ethyl acetate and diethylether.

If necessary, crystallisation may be initiated by seeding with the racemic crystalline diol acid addition salt.

According to a preferred embodiment of the invention, the free base of the *RS*-diol or the hydrochloride salt of the *RS*-diol is precipitated, preferably in crystalline form in steps i), iia) and iib).

The *R*- or *S*-diol may be isolated from the mother liquor using conventional procedures such as evaporation of the solvent from the mother liquor, or in case the

mother liquor is acidic by basification followed by separation of phases or by extraction of *R*- or *S*-diol followed by evaporation of the solvent.

R- or *S*-citalopram may be formed from the corresponding *R*- or *S*-diol by ring closure with retention of configuration. *S*-citalopram (or *R*-citalopram) may optionally be converted to an acid addition salt thereof, preferably the oxalate salt and optionally recrystallised.

It has been found that the enantiomeric purity (the ratio of the wanted isomer compared to the sum of both isomers) of the *S*- or *R*-diol left in the mother liquor may be as high as 97-98% or even better depending on the specific conditions used.

The mother liquor, extracts thereof, or a phase enriched with *R*- or *S*-diol may be subjected to conventional purification processes (such as treatment with active carbon, chromatography etc.) before evaporation of the solvent, and/or it may be subjected to one or more further precipitations of *RS*-diol free base or *RS*-diol acid addition salt according to the invention, in order to improve the enantiomeric purity of the diol enantiomer product.

The *S*-diol (or *R*-diol) prepared according to the invention may contain a minor amount of the *R*-diol (or *S*-diol). In one embodiment this minor amount may be less than 3%, or more preferred less than 2%, or most preferred less than 1%.

Enantiomerically-pure *R*- or *S*-diol may be mixed with a non-racemic mixture of *R*- and *S*-diol to obtain racemic diol. Racemic diol may then be obtained by one or more precipitations of racemic diol free base or an acid addition salt thereof, followed by recrystallisation as described above.

Ring closure of the *R*- or *S*-diol may be performed via a labile ester intermediate, e.g. in the presence of tosyl-chloride, in a basic environment, as described in EP-B1-347 066. Then, the ring closing reaction proceeds with retention of the stereochemistry. *R*- or *S*-citalopram of an enantiomeric purity substantially equal to the starting diol is then obtained.

Ring closure of the obtained racemic diol may be performed in an acidic environment, as described in US 4,650,884, or via a labile ester as described above. Thereby, racemic citalopram is obtained.

The thus-obtained enantiomerically-pure *R*- or *S*-citalopram may be mixed with a non-racemic mixture of *R*- and *S*-citalopram to obtain racemic citalopram. Racemic citalopram may then be obtained by one or more precipitations of citalopram free base or an acid addition salt thereof, followed by recrystallisation as described above.

According to another aspect of the invention, the initial non-racemic mixture of *R*- and *S*-diol is separated into a fraction being enriched with *S*-diol or *R*-diol and a fraction consisting of *RS*-diol wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol by adding the initial non-racemic mixture of *R*- and *S*-diol to a solvent and allowing preferentially the *R*- or *S*-diol to dissolve in the solvent followed by separation of the undissolved *RS*-diol residue from the said solvent or mother liquor and isolation of *R*- and *S*-diol from said solvent.

The solvent used according to this embodiment of the invention is any solvent which allow preferentially the *R*-or *S*-diol to dissolve leaving a mixture of *RS*-diol free base or an acid addition salt thereof wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol as a residue. Useful solvents are solvents such as those mentioned above for the precipitation of *RS*-diol free base and *RS*-diol acid addition salts.

The *R*-or *S*-diol may be purified and isolated form said solvent or mother liquor as described above.

The process may be repeated until a racemic mixture of *R*- and *S*-diols is obtained and/or until the desired degree of enantiomeric purity of the *R*- or *S*-diol is obtained.

Thus according to this aspect, the invention relates to a process for the preparation of racemic diol free base or an acid addition salt thereof and/or *R*- or *S*-diol as the free base or an acid addition salt thereof by the separation of an initial non-racemic mixture of *R*- and *S*-diol with more than 50% of one of the enantiomers into a fraction being enriched with *S*-diol or *R*-diol and a fraction consisting of *RS*-diol wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol **characterized in that**

i) *RS*-diol is precipitated from a solvent as the free base or as an acid addition salt thereof; or
R- or *S*-diol is dissolved into a solvent from the initial non-racemic mixture of *R*- or *S*-diols as the free base or as an acid addition salt thereof contained in said solvent, leaving a residue hereafter referred to as the precipitate;

ii) the precipitate formed is separated from the mother liquor;

iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;

iib) if the precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline precipitate is obtained and the crystalline precipitate is optionally recrystallised one or more times to form racemic diol;

iii) the mother liquor is optionally subjected to further purification and *S*-diol or *R*-diol is isolated from the mother liquor;

iv) the free bases of the diols obtained are optionally converted to acid addition salts thereof or acid addition salts of the diols obtained are optionally converted to other acid addition salts or acid addition salts of the diols obtained are optionally converted to the corresponding free bases.

The invention is illustrated by the following examples, which may not be construed as limiting.

Examples

In the following examples optical purity is measured by Chiral SCFC (super critical fluid chromatography) HPLC.

Example 1

Purification of *S*-diol by precipitation of racemic diol as the hydrochloride salt

General method:

A mixture of *R*- and *S*-diols (as defined in the table below) (10 g) was dissolved in toluene (60 mL). Aqueous hydrochloric acid solution (32 mL, 1 M) was added, and in some cases solid sodium chloride was added (enough so that the concentration of NaCl in the water was approximately 1 M). The mixture was stirred overnight, and filtered. The residue was dried to give crystals of racemic diol hydrochloride, contaminated by some *S*-diol hydrochloride. The mother liquor was basified with aqueous ammonia solution to pH > 9, and the toluene layer was separated. The aqueous layer was washed once more with toluene, and the combined toluene extracts were dried over magnesium sulfate and evaporated under reduced pressure to give mainly *S*-diol, contaminated with a small amount of *R*-diol. See table for details. Recovery of material was virtually quantitative, with the expected partitioning of weight between the respective samples.

Before Precipitation		After Precipitation			
Mixture of Isomers		Precipitate (mixture of R and *S*-diols		Oil after basification, separation and evaporation (enriched *S*-enantiomer)	
S%	R%	S%	R%	S%	R%
98.4	1.6	54	46	97.9	2.1*
95.4	4.6	55	45	98.7	1.3*
90.3	9.7	51	49	96.7	3.3
80	20	51	49	96.7	3.3
69	31	50	50	94.8	5.2
59	41	54	46	92	8.0

*Denotes that solid NaCl was added to the mixture, sufficient so that the resulting water phase was approximately 1 M in NaCl.

In the following examples optical purity is measured by Chiral HPLC.

Example 2

Purification of *S*-diol by precipitation of racemic diol free base

A solution of *S*-diol in acetonitrile (500 mL, *ca.* 50 – 55% w/w, *S*:*R* ratio 95.72:4.28) at room temperature was cooled with stirring to –14 °C. The mixture was seeded with almost-racemic diol (*S*:*R* ratio *ca.* 60:40) after every drop in temperature of 2 °C. After 16 hours the mixture was filtered, and the filter cake was dried. Analysis of the filter cake indicated that the *S*:*R* ratio was 57.97:42.03. Analysis of the mother liquor indicated that the *S*:*R* ratio was 98.065:1.935.

Example 3

Purification of *S*-diol by precipitation of racemic diol free base

A solution of *S*-diol in acetonitrile (500 mL, *ca.* 50 – 55% w/w, *S*:*R* ratio 95.72:4.28) at room temperature was cooled with stirring to –10 °C with cooling at a rate of 1 °C/h. The mixture was seeded with almost-racemic diol (*S*:*R* ratio *ca.* 60:40) after every drop in temperature of 5 °C. After 40 hours at –10 °C the mixture was filtered, and the filter cake was dried. Analysis of the filter cake indicated that the *S*:*R* ratio was 59.19:40.81. Analysis of the mother liquor indicated that the *S*:*R* ratio was 98.52:1.48.

Claims:

1. A process for the preparation of racemic diol free base or an acid addition salt thereof and/or *R*- or *S*-diol as the free base or an acid addition salt thereof by the separation of an initial non-racemic mixture of *R*- and *S*-diol with more than 50% of one of the enantiomers into a fraction being enriched with *S*-diol or *R*-diol and a fraction consisting of *RS*-diol wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol **characterized in that**

   i) *RS*-diol is precipitated from a solvent as the free base or as an acid addition salt thereof;

   ii) the precipitate formed is separated from the mother liquor;

      iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;

      iib) if the precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline precipitate is obtained and the crystalline precipitate is optionally recrystallised one or more times to form racemic diol;

   iii) the mother liquor is optionally subjected to further purification and *S*-diol or *R*-diol is isolated from the mother liquor;

   v) the free bases of the diols obtained are optionally converted to acid addition salts thereof or acid addition salts of the diols obtained are optionally converted to other acid addition salts or acid addition salts of the diols obtained are optionally converted to the corresponding free bases.

2. A process according to claim 1 for the preparation of *S*-diol or *R*-

diol characterized in that

i) *RS*-diol is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor, and

iii) the mother liquor is optionally subjected to further purification and *S*-diol or *R*-diol is isolated from the mother liquor.

3. A process according to claims 1 or 2 wherein the diol prepared is the S-diol.

4. A process according to claim 1 for the preparation of racemic diol characterized in that

i) *RS*-diol is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor,

iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;

iib) if the precipitate is not crystalline, steps i) and ii) are repeated until a crystalline precipitate is obtained and the crystalline precipitate is optionally recrystallised one or more times to form racemic diol.

5. The process according to any of claims 1-4 wherein the mixture of *R*- and *S*-diol with more than 50% of one of the enantiomers contains more than 50% of *S*-diol, more preferred more than 70% of *S*-diol or most preferred more than 90% of *S*-diol.

6. The process according to any of claims 1-5 wherein the acid used for precipitating *RS*-diol as a salt in step i) is an acid which precipitates a mixture of the *R*- and *S*-enantiomers and leaves the mother liquor enriched with either the *S*- or *R*-enantiomer of the diol.

7. The process according to any of claims 1-6 wherein the acid used for precipitating *RS*-diol as a salt in step i) is HCl or HBr, H_2SO_4 or oxalic acid.

8. The process according to any of claims 1-7 wherein the hydrochloride salt of the *RS*-diol is precipitated in step i), preferably in crystalline form.

9. The process according to any of claims 1-5 wherein the free base of the *RS*-diol is precipitated in step i), preferably in crystalline form.

10. The process according to any of claims 1-3 and 5-9 wherein the *S*-diol (or *R*-diol) is isolated from the mother liquor by evaporation of the solvent.

11. The process according to any of claims 1-3 and 5-9 wherein the mother liquor is acidic and the *S*-diol (or *R*-diol) is isolated from the mother liquor by basifying the mother liquor, followed by phase separation or extraction with a solvent followed by evaporation of the solvent.

12. The process according to any of claims 1-3 and 5-11 wherein the *S*-diol (or *R*-diol) obtained contains a minor amount of the *R*-diol and *S*-diol respectively such as less than 3 %, more preferred less than 2 %, or most preferred less than 1%.

13. The process according to any of claims 1-3, and 5-11 wherein the mother liquor is subjected to one or more further precipitations of *RS*-diol as described under step i) before isolation of the *S*-diol or (*R*-diol) from the mother liquor.

14. Use of the diol prepared according to any of claims 1-13 for the preparation of the corresponding citalopram or escitalopram.

15. A method for the preparation of citalopram or escitalopram comprising preparation of racemic diol or S-diol according to any of claims 1-13 followed by ring closure.

16. A method according to claims 1-5 and 9-13 wherein the *RS*-diol free base is precipitated from a solvent selected from alkanes, such as heptane or hexane, aromatic hydrocarbons such as toluene, benzene and xylene, or polar solvents such as acetonitrile.

17. A method according to claims 1-8 and 10-13 wherein the *RS*-diol acid addition salt is precipitated from a solvent selected from toluene, ethylacetate and diethylether.

Abstract

The invention relates to a process for the preparation of racemic diol free base or an acid addition salt thereof and/or *R*- or *S*-diol as the free base or an acid addition salt thereof by the separation of an initial non-racemic mixture of *R*- and *S*-diol with more than 50% of one of the enantiomers into a fraction being enriched with *S*-diol or *R*-diol and a fraction consisting of *RS*-diol wherein the ratio of *R*-diol:*S*-diol is equal to 1:1or closer to 1:1 than in the initial mixture of *R*- and *S*-diol **characterized in that**

i) *RS*-diol is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor;

iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;

iib) if the precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline precipitate is obtained and the crystalline precipitate is optionally recrystallised one or more times to form racemic diol;

iii) the mother liquor is optionally subjected to further purification and *S*-diol or *R*-diol is isolated from the mother liquor;

iv) the free bases of the diols obtained are optionally converted to acid addition salts thereof or acid addition salts of the diols obtained are optionally converted to other acid addition salts or acid addition salts of the diols obtained are optionally converted to the corresponding free bases.